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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,651	07/12/2001	Hiroyuki Nakane	77670/495	2816

7590 08/22/2006

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,651	NAKANE ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/31/06, 6/21/06, and 6/23/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 33-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 33-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/898,560.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/2/2006 has been entered.

[2] The numbering of claims is not accordance with 37 CFR 1.73(e). The preliminary amendment filed on 7/12/2001 adds claims 19-34, however, it is noted that the numbering of claims in this preliminary amendment failed to comply with 37 CFR 1.173(e), and claims 19-34 were re-numbered as claims 17-32. See particularly paragraph [3] at page 2 of the Office action mailed on 9/29/2004. Because claims 33-34 have yet to be presented for examination on the merits, claims 35-50 are misnumbered and have been renumbered as claims 33-48.

[3] Claims 1-16 and 33-48 are pending in the application.

[4] Applicant's amendment to the claims, filed on 6/2/2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[5] As noted in the Office communication mailed on 6/26/2006, the Notice of Non-Compliant Amendment mailed on 6/9/2006 was sent in error for reasons noted therein.

[6] Applicant's arguments filed on 3/31/2006 in response to the Office action mailed on 1/3/2006, applicant's arguments filed on 6/2/2006 in response to the Office action

mailed on 4/18/2006, and applicant's arguments filed on 6/23/2006 in response to the Office communication mailed on 6/9/2006 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[8] The objection to the specification under 35 U.S.C. § 251 as introducing new matter by way of the specification amendment filed on 3/18/2005 is withdrawn.

In the instant response at p. 13, applicant presents a comparison of the possible permutations of the region II sequence of claim 1, *i.e.*, $D_1D_2X_1X_2(X_3X_4)D_3$, and the region II sequence of claim 35, *i.e.*, $D_1D_2X_1(X_2X_3)X_4D_3$. The comparison appears to be exhaustive and further appears to corroborate applicant's admission on the record that "these algorithms encompass the exact same genus of sequences" and applicant's further admission that "the parenthesis in the algorithm creates no change in the genus of amino acid sequences encompassed therein." Because the scope of sequences of region II of claim 1 is the same as that of the scope of sequences of region II, it would appear that the specification provides adequate support for the limitation of $D_1D_2X_1(X_2X_3)X_4D_3$ as set forth in the claims. Thus, in view of applicant's comparison

between the algorithms and applicant's admitted sameness between the two, the rejection is withdrawn.

Claim Objection

[9] Claims 8 and 33 are objected to as being in an improper format. Applicants are advised that amendments to the specification should meet the requirements of 37 CFR 1.173(b)(2). Applicants are advised that future claim amendments should comply with the requirements of 37 CFR 1.173(b)(2). Applicants are further advised that future amendments to the claims must be based on the original claims.

Regarding claim 8, it is noted that 37 CFR 1.173(d)(2) states (in relevant part), "[a]ny changes relative to the patent being reissued which are made to the specification, including the claims, upon filing, or by an amendment paper in the reissue application, must include the following markings...The matter to be added by reissue must be underlined." It is noted that "SEQ ID NO:1," which has been added by amendment, is not underlined.

Regarding claim 33, this claim has the parenthetical expression "(Amended)," however, claim 33 has yet to be presented and, in accordance with MPEP § 1453.V.C, the claim should include no parenthetical expression.

Claim Rejections - 35 USC § 112, Second Paragraph

[10] The rejection of claims 1-32 under 35 U.S.C. 112, second paragraph, as being confusing in the recitation of "said mutant...synthesizes prenyl diphosphate that is

shorter than prenyl diphosphate synthesized by a corresponding wild-type" is withdrawn in view of the amendment to claims 1 and 33 to recite "said mutant...synthesizes a greater amount of a prenyl diphosphate of a first chain length than is synthesized by a corresponding wild-type..." in lines 17-19 of claims 1 and 33. This limitation is in agreement with the disclosure of the invention, particularly the results of Figure 3, which show that the prenyl diphosphate that is synthesized by the disclosed mutant is identical in size to the prenyl diphosphate synthesized by the corresponding wild-type enzyme (¶ [21] of the 7/18/2005 Office action).

[11] The rejection of claims 1-32 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "region II" is withdrawn in view of the amendment to claims 1 and 33 to define "region II" as being "greater than about 25% homologous to positions 72 to 93 of SEQ ID NO:1." That region II must comprise the aspartic acid rich domain as defined in claims 1 and 33 and be "greater than about 25% homologous to positions 72 to 93 of SEQ ID NO:1," a skilled artisan would recognize that portion of a polypeptide that applicant intends as being "region II."

[12] The rejection of claims 2, 16, and 18 under 35 U.S.C. 112, second paragraph, as being unclear in the recitation of "an enzymatic activity" is withdrawn in view of the amendment to claims to define the "activity" as "synthesizes about as much or more prenyl diphosphate than the amount of prenyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions."

Claim Rejections - 35 USC § 112, First Paragraph

[13] Claims 1-16 and 33-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" (MPEP 8th Ed., October 2006 Revision at pp. 2100-176 and 2100-183) and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

According to applicant at pp. 8 and 15 of the instant response, support for claim 1 can be found in original claim 1, Figure 1 and description thereof, Examples 1 and 4 (see p. 8 of the instant response), and in the references of Chen et al. (*Prot Sci* 3:600-607) and Kelly (available via internet at www.chemcomp.com/journal/families.htm; accessed on 1/18/06). At p. 16, top of the instant response, applicant argues that the percent homology limitation of claims 1 and 33 is supported by the disclosed prenyl diphosphate synthase polypeptide sequences and the teachings of Chen et al. and Kelly.

However, the examiner can find no express, implicit, or inherent support for all mutants as encompassed by the claims, particularly for the limitations of "wherein said region II...is greater than about 25% homologous with the sequence consisting of positions 72 through 93 of SEQ ID NO:1" as recited in lines 8-10 of claims 1 and 33 and "wherein said mutant...synthesizes a greater amount of a prenyl diphosphate of a first chain length than is synthesized by a corresponding wild-type...and wherein said wild-type prenyl diphosphate synthase may or may not synthesize said prenyl diphosphate of said first chain length" as recited in lines 17-27 of claim 1 and in lines 17-26 of claim 33 and the limitation of "synthesizes about as much or more prenyl diphosphate than the amount of prenyl diphosphate synthesized by the wild type prenyl diphosphate synthase under similar conditions" as recited in claims 2 and 34.

Claim 1 provides written support for the limitation "wherein said mutant...synthesizes prenyl diphosphate which is shorter than prenyl diphosphate synthesized by a corresponding wild-type." Figure 1 and its description describe certain amino acid sequences of prenyl diphosphate synthase polypeptides. Example 1 discloses the cloning of the SacGGPS gene and Example 4 describes mutation of particular nucleotides of the SacGGPS gene to generate specific amino acid variants. The combination of this disclosure, while it may provide support for certain specific mutants of SEQ ID NO:1 as provided in the instant disclosure, fails to provide adequate support for the limitations as set forth above. The teachings of Chen and Kelly fail to cure the lack of adequate support for the limitations at issue.

In the advisory action mailed on 4/18/2006, the examiner noted that, in denying entry of the after-final amendment mailed on 3/31/2006, the limitation of "greater than about 25% homologous with the sequence comprising positions 72 through 93 of SEQ ID NO:2" was not supported by the original application and would appear to raise the issue of new matter under 35 USC 112, first paragraph. Such limitation is essentially reproduced in claims 1 and 33 of the claims as submitted in the amendment filed on 6/2/2006. In the response filed on 6/2/2006, applicant addresses the examiner's comment regarding new matter by arguing: 1) the specification discloses five working examples of mutant polypeptides that satisfy the "greater than about 25% homologous" limitation; 2) Figure 1 discloses ten wild-type sequences of polypeptides from widely divergent sources that satisfy the "greater than about 25% homologous" limitation; the 5 mutant and 10 wild-type sequences that satisfy the "greater than about 25% homologous" limitation have been "fully correlated with the prenyl diphosphate synthase function"; 4) in view of the 15 working examples that are correlated with prenyl diphosphate function, a skilled artisan would recognize applicant was in possession of the genus of mutant polypeptides as encompassed by the claims; and 5) region II of a prenyl diphosphate synthase was known in the art as supported by the specification's disclosure of five representative species of wild-type prenyl diphosphate synthases and the reference of Chen.

Applicant's argument is not found persuasive. In evaluating claims for new matter, MPEP § 2163 states, "there is no *in haec verba* requirement" for newly added claim limitations, only that "newly added claim limitations must be supported in the

specification through express, implicit, or inherent disclosure" (MPEP 8th Ed., October 2005 Revision, p. 2100-175). According to the same section of the MPEP, "[t]he fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 156364, 19 USPQ2d at 1117." There is no dispute that the specification discloses 5 representative species of mutant prenyl diphosphate synthase polypeptides having at least 25% homology ("homology" interpreted herein as "identity") with amino acids 72 to 93 of SEQ ID NO:1. It should be noted that the 10 wild-type sequences referred to by applicant are not encompassed by the claims, which are drawn to *mutant* polypeptides. In this case, the five specifically-disclosed mutant polypeptides are insufficient to provide written support for a broad genus of mutant prenyl diphosphate synthase polypeptides that are "greater than about 25% homologous to amino acids 72 to 93 of SEQ ID NO:1." The teachings of Chen fail to cure the lack of adequate support for the limitations at issue.

Applicant is invited to show support for such limitations as noted above.

[14] The new matter rejection of claim(s) 17-32 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's argument. In the instant response at p. 13, applicant presents a comparison of the possible permutations of the region II sequence of claim 1, *i.e.*, $D_1D_2X_1X_2(X_3X_4)D_3$, and the region II sequence of newly added claim 33, *i.e.*, $D_1D_2X_1(X_2X_3)X_4D_3$. The comparison appears to be exhaustive and further appears to corroborate applicant's admission on the record that "these algorithms encompass the

exact same genus of sequences" and that "the parenthesis in the algorithm creates no change in the genus of amino acid sequences encompassed therein." MPEP § 2163 states that "there is no *in haec verba* requirement" for newly added claim limitations, only that "newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure" (MPEP 8th Ed., October 2005 Revision, p. 2100-175). According to the same section of the MPEP, "[t]he fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d at 156364, 19 USPQ2d at 1117." Because the scope of sequences of region II of claim 1 is the same as that of the scope of sequences of region II, it would appear that the specification provides adequate support for the limitation of $D_1D_2X_1(X_2X_3)X_4D_3$ as set forth in the claims. Thus, in view of applicant's comparison between the algorithms and admitted sameness between the two, the rejection is withdrawn.

[15] The new matter rejection of claim(s) 7 and 16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. Newly added claim 39 is included in the instant rejection. Thus, claims 7, 16, and 39 are rejected. The rejection was fully explained in previous Office actions.

RESPONSE TO ARGUMENT: Applicant argues support for the mutant enzymes of claims 7 and 39 can be in Figure 2 and the description thereof at column 5, lines 7 to 14.

Applicant's argument is not found persuasive. Claims 7 (claim 16 dependent therefrom) and 39 recite "[a] mutant enzyme...at least as thermostable as the corresponding wild-type...," thereby encompassing a mutant having any amino acid sequence as encompassed by the claims having an essentially unlimited enhanced thermostability as compared to wild-type. In this case, the cited disclosure fails to provide support for the limitation at issue. Figure 2 of the '832 patent shows the effects of specific mutations within the sequence of SEQ ID NO:1 on catalytic activity as a function of temperature over a defined temperature range. Contrary to applicant's assertion, the particular species of mutants as shown in Figure 1 fail to support the broader genus of mutants of claims 7 and 39. It is suggested that applicant show support for the limitation at issue.

[16] The written description rejection of claim(s) 1-7, 10, and 15-16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. Newly added Claims 33-39, 42, and 47-48 are included in the instant rejection. Thus, claims 1-7, 10, 15-16, 33-39, 42, and 47-48 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims are highly structured and the scope of the claims is strictly delimited beyond the minimal sequence limitations recited in the claims because: 1) the claims are directed to an enzyme that has prenyl diphosphate synthase activity and the specification and prior art disclose a representative number of prenyl diphosphate synthase polypeptides to show

possession; 2) the specification discloses five mutant species as encompassed by the claims and provides working examples of the claimed mutant; 3) the minimally recited structural feature is not intended to suggest that it imparts enzymatic activity, but to impart modification to the enzymatic activity; 4) in view of all recited elements of the claims, the polypeptide has enzymatic activity as evidenced by the reference of Chen et al.; and 5) the scope of the claims is limited to those mutants that are enzymatically active.

Applicant's argument is not found persuasive. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." While it is acknowledged that the *Lilly* Court's statements are directed to a genus of nucleic acids and not to a mutant polypeptide, the Court in *University of Rochester v. GD Searle & Co.* (358 F.3d 916) held this distinction to be "irrelevant," stating that "the statute applies to all types of inventions" and that "[w]e see no reason for the rule to be any different when non-genetic materials are at issue." In this case, the specification fails to either disclose a representative number of mutant prenyl diphosphate synthase polypeptides as encompassed by the claims or recite a substantial structural feature that is common to all members of the genus.

Regarding a representative number of species, according to MPEP § 2163, a "representative number of species" means that the species which are adequately

described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus." The disclosed representative species, all mutants of SEQ ID NO:1, wherein the mutation is limited to substitution at residues 77, 78, 80, 81, and 84 and an insertion between residues 84 and 85, fail to reflect the structural and functional variation among the species of claimed mutants, which, with regard to structural variability, encompasses any mutant prenyl diphosphate synthase polypeptide having the activities as defined in lines 17-26 of claims 1 and 33 and having any amino acid sequence as long as it has the minimal structural features as recited in lines 3-16 of claims 1 and 33, and with regard to functional variability, encompasses species that have the ability to produce any prenyl diphosphate in a greater amount relative to wild-type. It is further noted that the substitution must result in the recited activity as defined in lines 17-27 of claims 1 and 33 and, other than the disclosure of those specific mutations of SEQ ID NO:1, the specification and the prior art fail to disclose any other structural mutations within the sequence of SEQ ID NO:1 or any other prenyl diphosphate synthase from other sources that results in the recited functionality. The examiner acknowledges that the claims are directed to an enzyme, not the sequence thereof. However, it is the amino acid *sequence* of the polypeptide that imparts functionality to the polypeptide. Thus, it is the examiner's position that the specification fails to disclose a representative number of mutant prenyl diphosphate synthase polypeptides as encompassed by the claims.

Regarding a shared structural feature, it is noted that claims 1 and 33 recite two common structural features that are shared among the members of the genus of claimed mutant enzymes, *i.e.,* all members of the genus are required to have the aspartic acid rich domain of $D_1D_2X_1X_2(X_3X_4)D_3$ or $D_1D_2X_1(X_2X_3)X_4D_3$ as defined in the claims and have greater than about 25% homology with amino acids 72 to 93 of SEQ ID NO:1. Given that art-recognized sequences of prenyl diphosphate synthase polypeptides are approximately 350 amino acids in length as evidenced by Chen et al. (p. 602, Figure 2) and thus an enzymatically active polypeptide would require approximately 350 amino acids to achieve the recited function, such a structural feature as recited in the claims would not be considered to "constitute a substantial portion of the genus" of claimed mutant enzymes. Indeed, outside of the recited structural features, the sequence of the polypeptide is completely undefined in the claims and can have any other amino acid mutation or variation that results in the recited functions. While the examiner acknowledges species of wild-type prenyl diphosphate synthase polypeptides were known in the art at the time of the invention, the claims are not limited to maintaining wild-type sequence outside of the recited structural features and the claims have not been so narrowly interpreted.

Consequently, the specification fails to describe all members of the claimed genus of proteins and nucleic acids.

[17] The scope of enablement rejection of claims 8-9, 11-13, 24-25, and 27-29 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to claims 1 and

33 to replace the recited activity of the mutant enzyme from synthesizing a prenyl diphosphate that is shorter than that of wild-type to the activity as defined in lines 17-26 of claims 1 and 33. As noted in the prior Office action, while the specification provides evidence that the mutants can produce relatively *greater* amounts of farnesyl diphosphate as compared to the corresponding wild-type, there is no indication in the specification that the mutants have the ability to synthesize farnesyl diphosphate that has a *shorter chain length* than the farnesyl diphosphate synthesized by a corresponding wild-type enzyme (see particularly Figure 3).

[18] The scope of enablement rejection of claim(s) 1-7, 10, and 14-16 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action. Newly added Claims 33-39, 42, and 46-48 are included in the instant rejection. Thus, claims 1-7, 10, 14-16, 33-39, 42, and 46-48 are rejected.

RESPONSE TO ARGUMENT: Applicant argues working examples of the claimed mutants are disclosed as well as a number of wild-type prenyl diphosphate synthase sequences, which, according to applicant, would support an enabling disclosure. Applicant argues the claims are of narrow scope, the specification and prior art disclose sufficient guidance and working examples, there is a high level of predictability as evidenced by Kelly because the sequences of prenyl diphosphate synthases are highly conserved, and the experimentation required to screen for all mutants as encompassed by the claims is not undue.

Applicant's argument is not found persuasive. The examiner maintains the position that the specification fails to enable the full scope of the claimed invention. As noted in a previous Office action, the claims broadly encompass any mutant prenyl diphosphate synthase polypeptide having the ability to produce any prenyl diphosphate in a greater amount relative to wild-type and having any additional mutation outside of the structural features as recited in lines 3-16 of claims 1 and 33. As noted above, the reference of Chen et al. would suggest that prenyl diphosphate synthase polypeptides are of approximately 350 amino acids (p. 602, Figure 2). Thus, the claims encompass numerous mutations outside of the recited structural feature of claims 1 and 33. In this case, the specification discloses only five working examples of the claimed polypeptides, wherein the five working examples have the activity to produce greater amounts of farnesyl diphosphate relative to wild-type (see particularly Figure 3). Further, it is noted that the specification discloses that the host organism of claims 14 and 46 broadly encompasses a plant (column 7, lines 44-45). In this case, the specification fails to provide guidance for making other mutant enzymes within the scope of the claims, which is undisputed by applicant and further fails to provide any guidance for making a transgenic plant. Further, the prior art references of Branden and Witkowski et al. support a high level of unpredictability in the art. While applicant asserts the reference of Kelly contradicts the teachings of Branden and "demonstrates great strides in the artisan's understanding of the protein structure and function between 1991 and 1997," the cited teaching of the reference of Kelly, *i.e.,* that "if a protein sequence shares more than 25% pairwise similarity with a known structure, it usually also shares at least the

broad outlines of the fold topology of the known structure" (introduction at paragraph 1), would not appear to go against the teachings of Branden et al. The remark by Kelly appears to be directed to polypeptides that share 25% homology over the full length of their sequences. However, in this case, there is no requirement that the mutant and SEQ ID NO:1 share 25% homology over the full length of their sequences – only that region II is greater than about 25% homologous to amino acids 72 to 93, or 22 amino acids, of SEQ ID NO:1, which, according to the sequence listing, is 330 amino acids. Furthermore, the remarks of Kelly appear to be directed to wild-type sequences, which have been naturally selected for their ability to maintain a certain function, and thus would not appear to relate to mutant sequences. Furthermore, even assuming *arguendo* the mutant polypeptide shared "at least the broad outlines of the fold topology of the known structure" of SEQ ID NO:1, it is noted that this is no indication that the mutant polypeptide would maintain the desired activity as recited in the claim. As such, the teachings of Kelly do not contradict the teachings of Branden et al. and Witkowski et al., which support a high level of unpredictability in the art at the time of the invention. Regarding the "host organism" of claims 14 and 46, it is noted that even as late as 2002, the art recognizes a high level of unpredictability in making a transgenic plant (see Vain et al. *Theor Appl Genet* 105:878-889, particularly p. 878, right column, top). In view of the broad scope of claimed variants, the lack of guidance and working examples, and the high level of unpredictability in the art, a skilled artisan is left to screen for all mutants with any mutation as encompassed by the claims and additionally having any mutation outside of "region II" for those that can synthesize any prenyl

diphosphate synthase in an amount greater than wild-type and all host organism as broadly encompassed by the claims. While methods of generating variants of a given polypeptide are known in the art, *e.g.,* mutagenesis, it was not routine in the art to screen for *all* polypeptides having a substantial number of substitutions or modifications as encompassed by the instant claims for those that have the desired activity. Also, it was not routine to attempt to transform all host organisms – including a plant – to screen for those that can successfully be transformed and express the encoded polynucleotide.

In view of the broad scope of the claims, the lack of guidance and working examples, the high level of unpredictability as supported by the prior art, and the significant amount of trial and error experimentation required, which was not typically practiced at the time of the invention, the specification fails to enable the full scope of the claimed invention without undue experimentation.

Double Patenting Rejection(s)

[19] The obviousness-type double patenting rejection of claims 1-6 and 8-10 as being unpatentable over claims 1 and 4 of US Patent 5,807,725 is maintained for the reasons of record. In view of the instant claim amendment, claims 7 and 33-42 are included in the instant rejection. Thus, claims 1-10 and 33-42 are rejected.

[20] The obviousness-type double patenting rejection of claims 11 and 13-15 as being unpatentable over claims 1-4 of US Patent 5,882,909 is maintained for the reasons of

record. In view of the instant claim amendment, claims 43 and 45-47 are included in the instant rejection. Thus, claims 11, 13-15, 43, and 45-47 are rejected.

RESPONSE TO ARGUMENT: Applicant asserts the double patenting rejections will be attended to at the time the claims are allowed. The examiner acknowledges applicant's remarks.

Conclusion

[21] Status of the claims:

- Claims 1-16 and 33-48 are pending.
- Claims 1-16 and 33-48 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656